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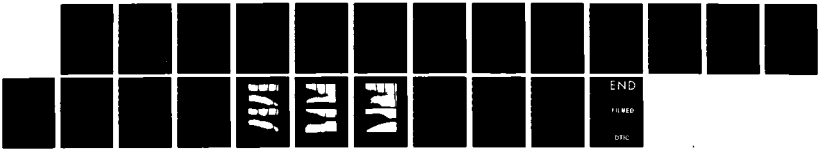

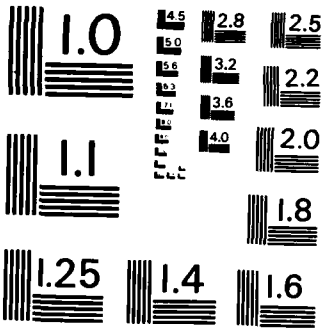

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APPLIED LABORATORY AND CLINICAL STUDIES ON BIODEGRADABLE CERAMIC

Annual Report

J. E. Lemons

March 1982

Supported by
U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract DAMD17-79-C-9173

University of Alabama in Birmingham
Birmingham, Alabama 35294

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Investigations on granular form tricalcium phosphate (TCP) and calcium hydroxylapatite (CaHA) ceramics and rod form tricalcium phosphate ceramic have continued in laboratory animal models. Segmental lesions at the middle region of rabbit tibiae that were filled with mixtures of TCP, CaHA and autogeneous bone showed healing and good biocompatibility. Eleven of twelve rabbits demonstrated biomechanical stability of the tibiae at euthanization.

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Rod form TCP segmental replacements at the middle region of dog radii showed residual TCP (radiographically) at four years post surgery. The animals continue without functional limitations.

Human clinical trials of granular form TCP and autogeneous bone have not been initiated at this time. Approval for this study is anticipated during 1982.

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SUMMARY

Laboratory investigations of segmental tibial lesion sites in rabbits showed healing and good biocompatibility for mixtures of granular form tricalcium phosphate (-40 + 100 mesh) and calcium hydroxylapatite (14 mesh) ceramics when mixed with autogeneous bone. Evaluations extended to nine months with eleven of twelve rabbits showing biomechanical stability of the tibiae. Long term studies of radii segmental replacements with porous rod form tricalcium phosphate in dogs shows residual material at four years post surgery. The animals remain fully functional without limitations of the use of the implanted limbs.

Initial human clinical studies on porous granular form tricalcium phosphate ceramic and autogeneous bone have been delayed.

FOREWORD

In conducting the research described in this report the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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INTRODUCTION

This report summarizes the results from the 1980-1981 program titled "Applied Laboratory and Clinical Studies on Biodegradable Ceramic", contract number DAMD17-79-C-9173.

The interest in the tricalcium phosphate ceramic (TCP) and calcium hydroxylapatite compounds for bone replacement continues at a quite high level.[1-3] The TCP has been introduced commercially for the treatment of periodontal lesions as has the particulate form of calcium hydroxylapatite.

Although new procedures and various types of replacement biomaterials continue to expand for major lesions of bone the basic methods of treatment continue to require reduction, mechanical stabilization, and autogeneous bone graft. To obtain a bone graft in many cases requires a second surgical procedure with the added possibilities of complications. The overall objective of the current program is to fully investigate one synthetic bone substitute material in an attempt to significantly improve the conditions for surgical correction of bone lesions. The military applications are extensive when considering the possibility of major reductions in maxillofacial and orthopaedic surgical time, deformities and morbidity.

The technical objectives of the programs summarized in this report were as follows:

1. To initiate limited human clinical trials utilizing autogeneous bone and/or granular form tricalcium phosphate ceramic.

2. To evaluate the feasibility of mixtures of granular tricalcium phosphate, granular hydroxylapatite and autogeneous bone for bone replacement in a laboratory animal model.

MATERIALS AND METHODS

Materials and Implant Fabrication

The porous TCP investigated was the material that has been used throughout this project. The details on the characterization of this substance were provided in a previous annual report*. The material was the granular form with a particulate size of -40 + 100 mesh. The hydroxylapatite was available from Sterling Winthrop Research Institute and was the 14 mesh particulate substance that has the trade name "Durapatite".

The materials were dry heat sterilized, in separate chambers at approximately 350°C for 1 hour in a muffle furnace.

*Contract Number DAMD17-75-C-5044, (1979).

Animal Models and Surgical Procedures

The segmental lesion that is created surgically and the stabilization pin arrangement for the rabbit tibia are shown schematically in Figure 1. This procedure has been described in detail in previous reports. For this series, the lesion was 8 mm length and the periosteum was retained at the lesion site. The relative quantities of the TCP and hydroxylapatite in equal amounts constituted 50 weight percent of the implant, with the other 50 percent of iliac crest autogeneous bone set at the surgery table using a beam balance.

The long term studies on the dog radius implants only include the follow up procedures. The dog radius animal model site is shown schematically in Figure 2. No surgical procedures were conducted on these animals during this reporting period.

Animal Follow Up

The rabbit and dog clinical follow up methods were very similar to those reported previously. In general, this includes general observation, routine radiographs, local implant site examinations, and selective corrective procedures where indicated.

Necropsy and Specimen Evaluations

The necropsy schedule placed most of the rabbits in the nine month post surgery group. After euthanization by drug overdose, the rabbit tibiae were dissected free of soft tissues, and the central implant sites were removed for standard histological and non-decalcified thin section studies.

None of the dogs were euthanized during this report period.

RESULTS AND DISCUSSION

Materials and Implant Fabrication

In general, no specific problems were encountered in fabricating, handling, sterilizing or placing the TCP or calcium hydroxylapatite materials.

Animal Models, Surgery and Follow Up

The rabbit and dog animal models continue to be quite acceptable for evaluating the feasibility of utilizing the ceramic materials in various forms. The rabbit tibia model provides a very good test of the material under conditions where a large number of similar evaluations have been conducted.

The surgical procedures were conducted without problems of significance. The granular substances tend to spread out of the immediate bone lesion region, but this has always been the case.

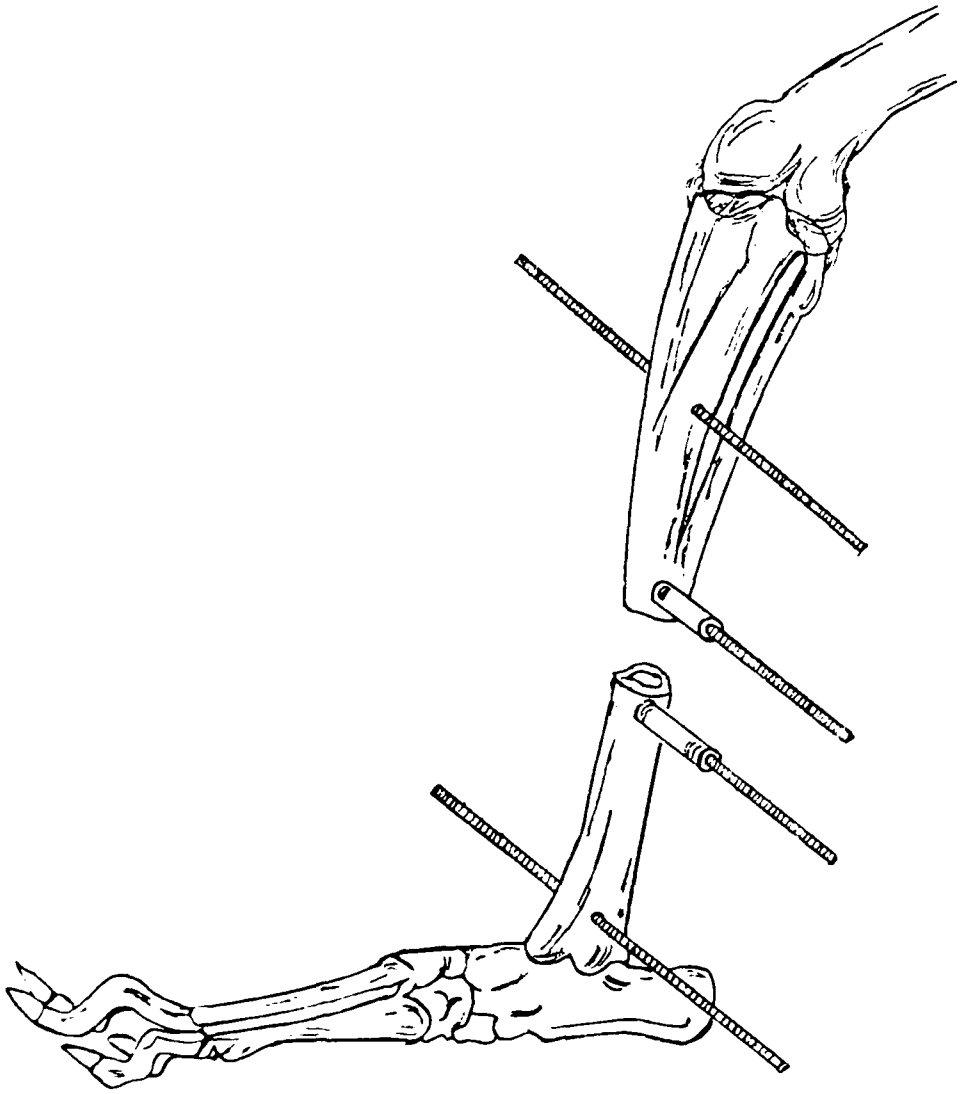

Figure 1. Schematic Drawing of Segmental Lesion in a Rabbit Tibia Showing the Relative Placement Positions of the Stabilization Pins

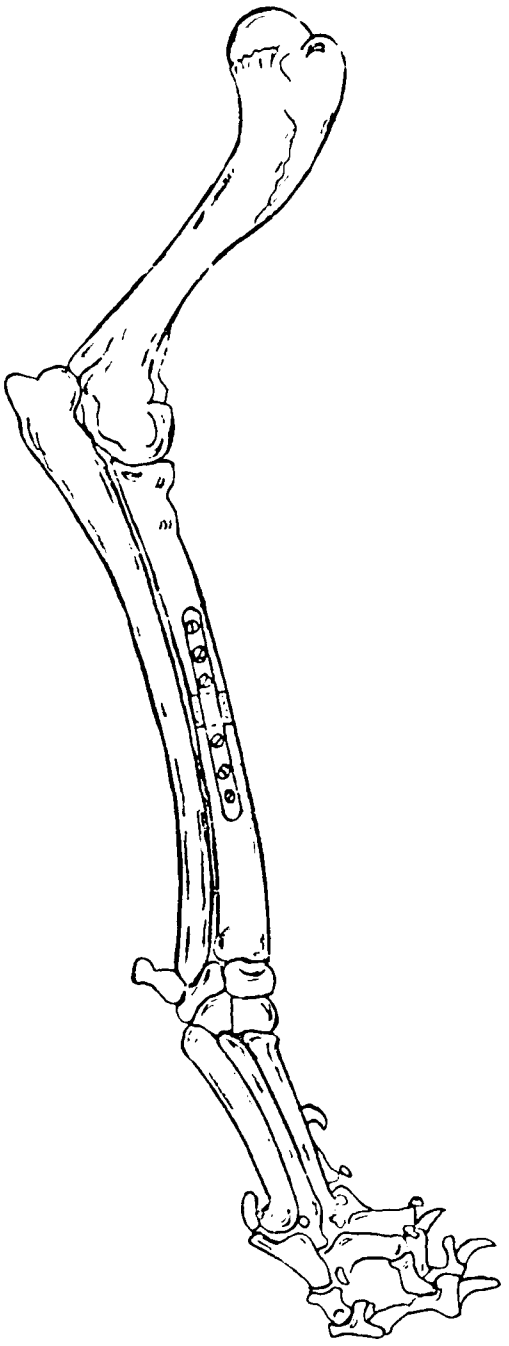

Figure 2. Schematic Drawing of the Segmental Bone Replacement and Bone Stabilization Plate for the Dog Studies

The follow up procedures on the rabbits continue to show the continuing problems of using caged animals for surgical research. However, the follow up statistics and problems were not different than in previous studies. The importance of having a veterinarian on the laboratory staff is very critical to minimizing possible problems.

Necropsy and Specimen Evaluations

The summary information on the rabbit tibia implant series comparing the TCP, calcium hydroxylapatite and autogeneous bone combinations is shown in Table 1. The table includes the rabbit identification number, date of surgery, duration of the experiment, and comments about the course of follow up. Two rabbits died before scheduled euthanization, and one was lost from the animal room for unknown reasons. The animals that were lost by early death were replaced in the series, which provided twelve rabbits with greater than twelve week follow up. One of these twelve demonstrated a delayed union. Eleven showed no significant problems. One rabbit was euthanized at 12 weeks because of a tibial fracture during stabilization pin removal. Another was euthanized at 31 weeks because of an ear infection while the remaining 10 rabbits were euthanized at 35 to 37 weeks post surgery.

Radiographs of the lesion sites for rabbits 432, 436 and 439 are shown in Figures 3, 4 and 5 respectively. The stabilization pins were retained for rabbit 432, Figure 3, until euthanization. The lesion showed bridging and union, but a limited quantity of callus. The tibia was biomechanically stable at euthanization. Rabbit 436, Figure 4, showed more callus relatively and the pins were cut to remove the stabilization but not removed from the bone. This decision is often made depending upon the "tightness" of the pins and the probability of removal at euthanization or earlier without fracturing the bone. The course of follow up on rabbit 436 was uneventful and the tibia was biomechanically stable at euthanization. Rabbit 439, Figure 5, shows an example where the stabilization pins were removed at approximately six weeks post surgery. The tibia was biomechanically stable at euthanization.

The calcium hydroxylapatite particulate is evident in the radiographs, and initial evaluations show minimal biodegradation of this compound. Some TCP is retained at nine months, as has been found previously. In general, no problems with respect to biocompatibility were found. The TCP and calcium hydroxylapatite, when used in combination, do not appear to elicit any adverse tissue reactions.

The radius implants in the dogs continue without significant problems. The first series of these lesion sites will be at five years during the 1982 contract year and will be presented in the next annual report.

Human Investigations

The initial human investigations have not been started because of the delays in obtaining the new quantities of TCP and the difficulties with Federal Drug Administration approval. The TCP materials became available at the end of this contract year and therefore should not be a problem for the future studies.

TABLE I. TRICALCIUM PHOSPHATE, CALCIUM HYDROXYLAPATITE AND AUTOGENEOUS IMPLANT SERIES IN RABBITS

RABBIT #	SURGERY DATE	DURATION (WKS)	COMMENTS
430	01/14/81	1	01/19/81: Died of unknown illness (cause).
431	01/19/81	12	01/19/81: Excessive material medially. 03/04/81: Limited callus, not healed. 04/09/81: Tibia stable. Not much callus. 04/10/81: Tibia fractured @ implant site while removing pins. Sacrificed animal.
432	01/26/81	36	01/26/81: Post-op OK. 03/13/81: No callus medially. Lateral aspect looks bridged. 08/17/81: No callus medially. Thin callus laterally. 10/05/81: Rabbit sacrificed. Implant site appeared biomechanically stable.
433	02/06/81	36	02/06/81: Distal tibia fractured during surgery. Tibia looked poor. 03/24/81: Callus around fracture. Ankle fracture healing. 06/23/81: Removed pins. Began treatment with antibiotics. 06/26/81: Not much callus. Ankle infection still present. 10/21/81: Small amount of callus seen on medial aspect. Rabbit sacrificed. Moderate infection @ distal tibia fracture site.
434	02/06/81	35	02/09/81: Post-op OK. 03/24/81: Lesion may be bridged. 07/15/81: Rabbit treated with antibiotics for snuffles. 08/17/81: Lateral aspect of lesion has good bridging. 10/09/81: Rabbit died (unknown cause). Tibia appeared biomechanically stable.

TABLE I. TRICALCIUM PHOSPHATE, CALCIUM HYDROXYLAPATITE AND AUTOGENEOUS IMPLANT SERIES IN RABBITS (continued)

RABBIT #	SURGERY DATE	DURATION (WKS)	COMMENTS
435	02/09/81	36	02/09/81: Post-op OK. 03/24/81: Moderate infection @ pin sites. Lesion bridged posteriorly. 06/24/81: Callus bridged medially. Medium callus around implant material. 08/04/81: Treatment for dehydration and snuffles. 10/21/81: Callus formation increased on lateral aspect. Animal sacrificed. Tibia biomechanically stable.
436	02/11/81	36	02/11/81: Post-op looks good. 03/24/81: Not bridged. Slight infection in proximal region. 06/24/81: Callus and bridging is questionable. 07/15/81: Treatment for proximal pin tract infection. 10/21/81: Animal sacrificed. Callus on both aspects. Tibia biomechanically stable.
437	02/13/81	2	02/11/81: Post-op OK. 02/28/81: Rabbit died. Tibia retrieved.
438	02/23/81	37	02/23/81: Post-op OK. 04/09/81: Not bridged. 06/24/81: Medial anterior displacement of proximal tibia segment. Non-union. Moderate infection @ proximal pin. 11/12/81: Animal sacrificed. Non-union.
439	02/23/81	37	02/23/81: Post-op OK. 04/09/81: Lateral methacrylate missing. Moderate pin tract infection. Bridged callus. 04/10/81: Pins removed. Pin tract infections treated. 08/17/81: Thin callus laterally and medially. 11/12/81: Animal sacrificed. Tibia biomechanically stable.

TABLE I. TRICALCIUM PHOSPHATE, CALCIUM HYDROXYLAPATITE AND AUTOGENEOUS IMPLANT SERIES IN RABBITS (continued)

RABBIT #	SURGERY DATE	DURATION (WKS)	COMMENTS
440	02/27/81	37	02/27/81: Post-op OK. 03/13/81: Slight pin tract infection. 08/17/81: Callus formation good laterally. 11/12/81: Animal sacrificed. Lesion appears bridged. Tibia biomechanically stable.
441	03/04/81	31	03/04/81: Post-op OK. 04/27/81: Lesion bridged post/laterally. 06/24/81: Mature callus laterally. Strength questionable. 07/15/81: Treatment for snuffles. 09/02/81: Medial methacrylate missing. 10/05/81: Sacrificed due to severe ear infection. Good callus @ implant site. Lesion biomechanically stable.
442	03/04/81	36	03/04/81: Medial displacement of proximal segment, otherwise OK. 04/27/81: Callus appears solid, but bridging questionable. 06/24/81: Proximal pin missing. Slight displacement. 07/15/81: Treatment for proximal pin tract infection. 11/16/81: Animal sacrificed. Proximal tibia segment displaced medial/anteriorly. Well formed callus.
443	03/06/81		04/09/81: Animal lost to follow-up because of undetermined reasons.
444	03/06/81	36	03/06/81: Post-op OK. 04/27/81: Anterior displacement of proximal segment. Some callus. 06/24/81: Lesion bridged laterally, but not medially. 11/16/81: Lesion appears bridged. Callus on each side is thin. Animal sacrificed. Tibia is biomechanically stable.

Figure 3. Radiographs of Lesion Site for Rabbit 432 Showing the Post Surgical (Upper) and Seven Month (Lower) Conditions.

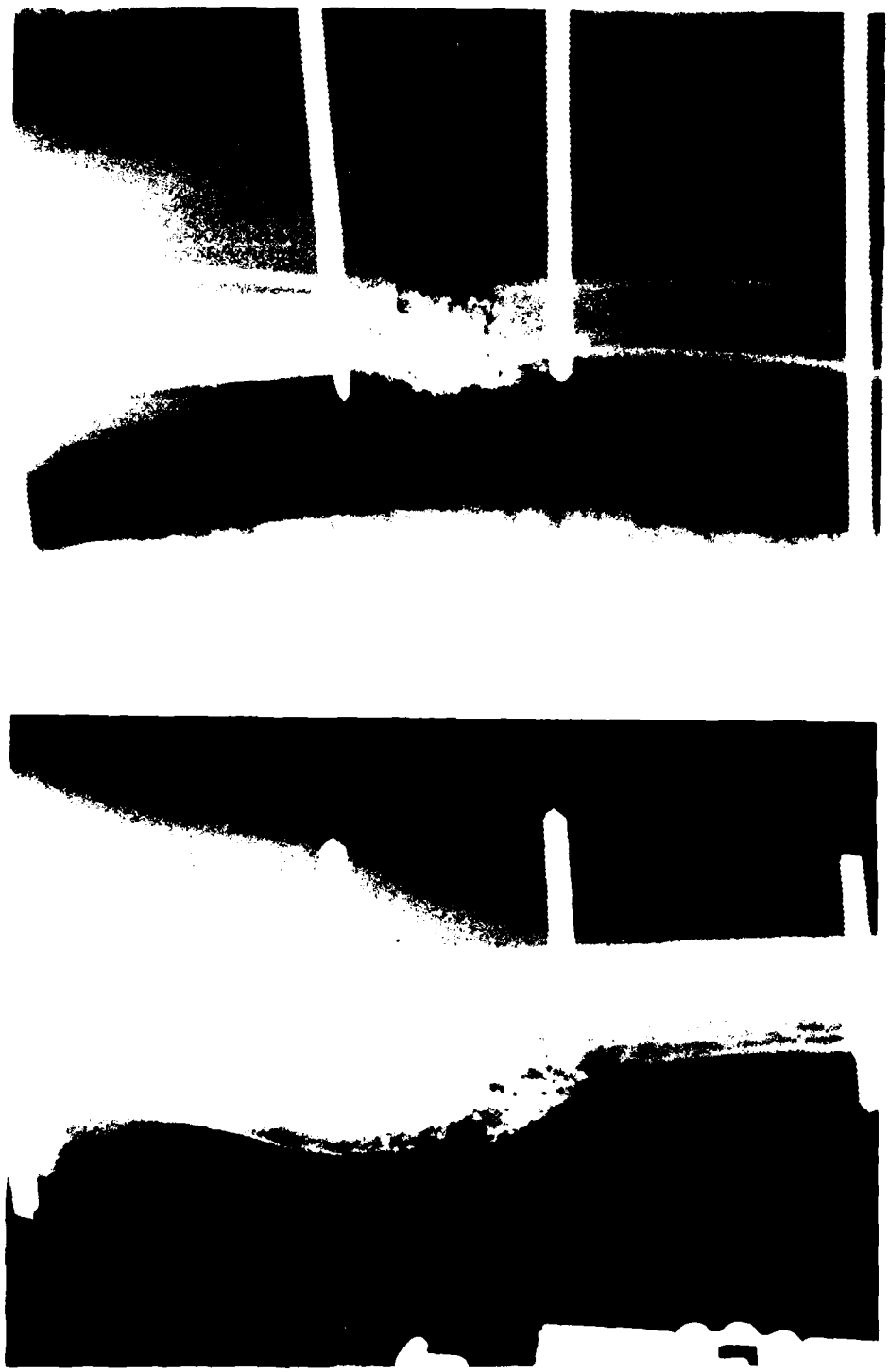

Figure 4. Radiographs of the Lesion Site for Rabbit 436 Showing the Post Surgical (Upper) and Eight Month (Lower) Conditions.

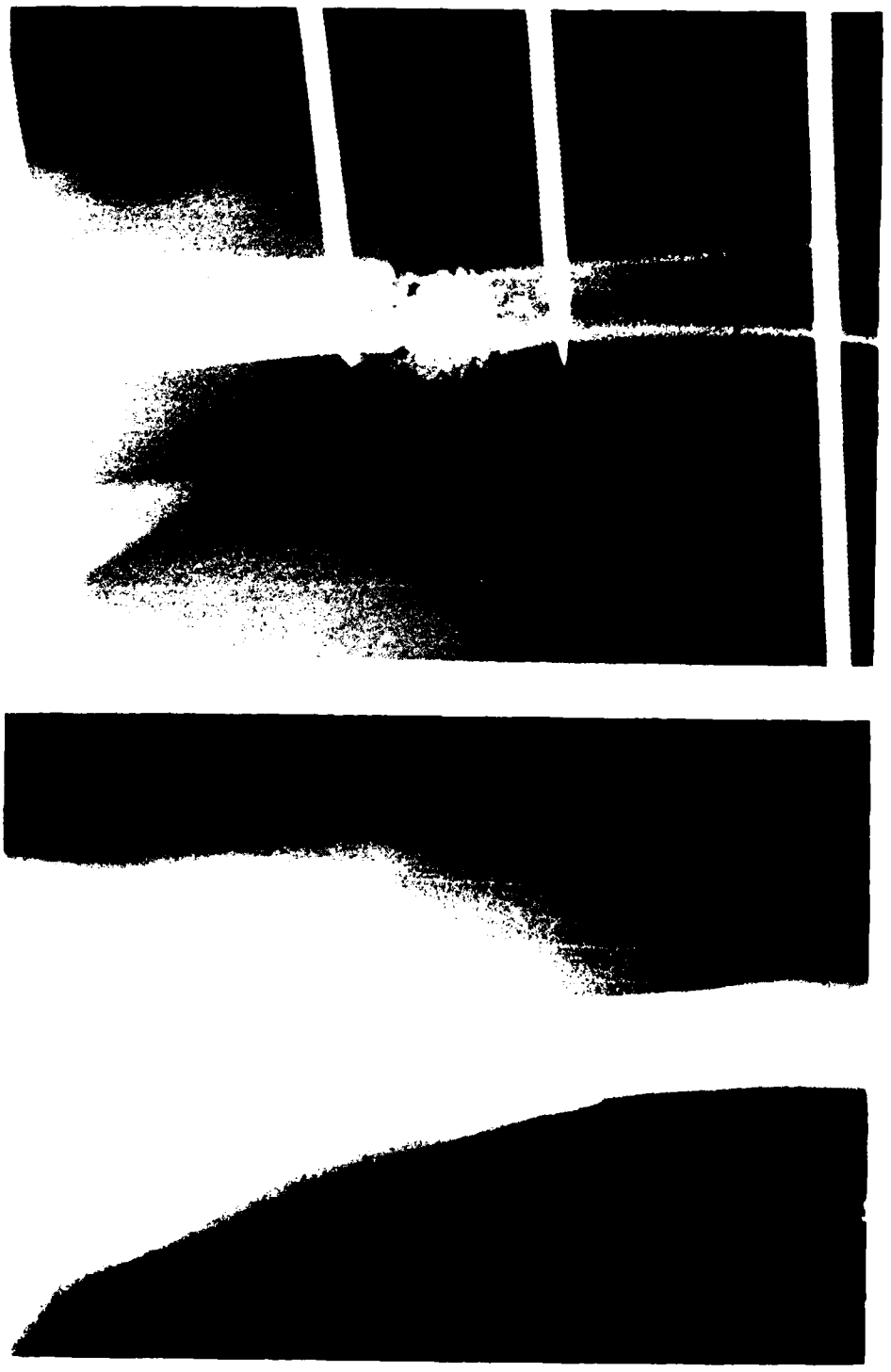

Figure 5. Radiographs of the Lesion Site for Rabbit 439 Showing the Post Surgical (Upper) and Nine Month (Lower) Conditions.

The FDA returned our applications to the main Washington offices without notification to our group, which subsequently resulted in another research group responding to the questions raised. This caused a significant delay. The application was eventually located with the questions and we have resubmitted for FDA consideration. The questions raised by the FDA were not restrictive, but rather were requests for additional information and copies of key references. This should be completed, in total, in the very near future. Because of the inability to obtain FDA approval, this phase of the proposed 1980-1981 program was not initiated.

CONCLUSIONS

The conclusions from the investigation conducted during the last year are summarized as follows.

1. Granular form tricalcium phosphate (-40 + 100 mesh) and calcium hydroxylapatite (14 mesh) ceramics when mixed with autogeneous bone and placed in 8 mm length rabbit tibial defects showed healing of the lesion for eleven of twelve rabbits.

2. The tricalcium phosphate and calcium hydroxylapatite granular form ceramics continue to show good biocompatibility.

3. The rod form tricalcium phosphate ceramic implants in dog radii continue to show biodegradation with all animals having functional utilization of the implanted limbs. Two sites are at four years post surgery and will be evaluated histologically during the next year.

4. The initial human clinical trials of the granular form tricalcium phosphate ceramic and autogeneous bone have been delayed by the formal review and approval process. Human trials could be initiated during 1982.

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3. Jarco, M., Calcium Phosphate Ceramics as Hard Tissue Prosthetics, J. Clin. Orthop. and Rel. Res., 157, (1981) pp 259.

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